

Connections

Building on:

- Carbonyl chemistry [ch6](#), [ch12](#), & [ch14](#)
- Conjugate addition [ch10](#)
- S_N1 and S_N2 reactions [ch17](#)
- Electrophilic aromatic substitution [ch22](#)

Arriving at:

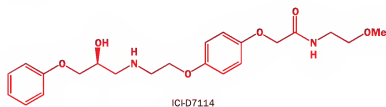
- Synthesis and retrosynthesis
- Thinking backwards
- How to make amines and ethers
- What are synthons?
- Choosing which C–C bonds to make
- Two-group disconnections are best
- Logical planning in enolate chemistry

Looking forward to:

- Diastereoselectivity [ch33–ch34](#)
- Pericyclic reactions [ch35–ch36](#)
- Synthesis of aromatic heterocycles [ch44](#)
- Asymmetric synthesis [ch45](#)
- Natural products [ch51](#)

Creative chemistry

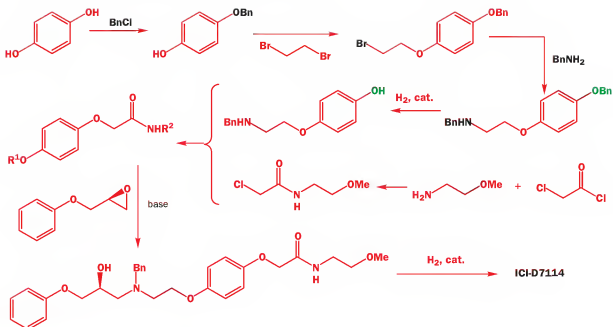
Chemistry is above all a creative science. Nearly all that you have learned so far in this book has had one underlying aim: to teach you how to make molecules. This is after all what most chemists do, for whatever reason. Small amounts of many drugs can be isolated from plants or marine animals; much greater quantities are made by chemists in laboratories. A limited range of dyes can be extracted from plants; many more vivid and permanent ones are made by chemists in the laboratory. Synthetic polymers, created by chemists, have replaced more expensive and less durable alternatives like rubber. Despite the bad press it has received, the use of PVC as insulating material for electric wires has prevented numerous fires and saved many lives. Eating is cheap and people live longer because pesticides allow agriculture to supply copious quantities of food to the shelves of our shops, markets, and supermarkets. Most of the improvements in the quality of life over the last 50 to 100 years can be traced to new molecules created by chemists.



But, faced with the challenge of making a new compound, how do chemists go about deciding how to make it? This molecule is known as ICI-D7114, and was identified as a possible anti-obesity drug. To test its efficacy, several hundred grams of it had to be made, and overleaf is how it was done.

The chemists who made this molecule could have chosen any route—any starting materials and any sequence of reactions. All that mattered was the final product—what we will call the target molecule. Synthetic planning starts with the product, which is fixed and unchangeable, and works backwards towards the starting materials. This process is called **retrosynthesis**, and the art of planning the synthesis of a target molecule is called **retrosynthetic analysis**. The aim of this chapter is to introduce you to the principles of retrosynthetic analysis: once you have read and understood it you will be well on the way to designing your own organic syntheses.

■ Of course, in a general text like this we are limited in the amount of detail we can cover—if you want to know more then read a specialized text.



▶ You now know four types of reaction arrow: the simple reaction arrow \rightarrow meaning 'reacts to give', the delocalization arrow \leftrightarrow meaning 'two different ways to draw the same delocalized structure', the equilibrium arrow \rightleftharpoons meaning 'these two structures are interconverting', and now the retrosynthesis arrow \Rightarrow meaning 'could be made from'.

▶ This chapter will rely heavily on the reactions you have met earlier in the book, and should therefore provide you with the opportunity to revise them and check you understand how they work. If you come across a reaction you aren't familiar with, look it up before carrying on to the next one.

Retrosynthetic analysis: synthesis backwards

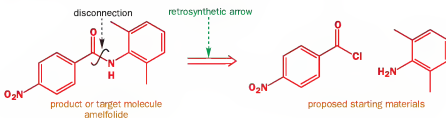
Much of the chemistry you have learned so far has concentrated on *reactions* (questions like 'what do you need to add to X to get Y?') or on *products* (questions like 'what will happen if X and Y react together?'). Now we're looking at *starting materials* (questions like 'what X and Y do you need to react together to make Z?'). We're looking at reactions in reverse, and we have a special symbol for a reverse reaction called a retrosynthetic arrow (the 'implies' arrow from logic).

A scheme with a retrosynthetic arrow $Z \Rightarrow X + Y$ means 'Z could be made from X plus Y'.

This compound is used as an insect repellent. As it's an ester, we know that it can be made from alcohol plus acyl chloride, and we can represent this using a retrosynthetic arrow.



The aromatic amide amelfolide is a cardiac antiarrhythmic agent. Because we see that it is an amide, we know that it can be made quite simply from *p*-nitrobenzoyl chloride and 2,6-dimethylaniline—again, we can represent this using a retrosynthetic arrow. Mentally breaking a molecule into its component parts like this is known as disconnection, and it's helpful to indicate the site of the disconnection with a wiggly line as we have here.

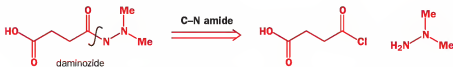


Disconnections must correspond to known, reliable reactions

The chemists who first made amefolide chose to make it from an amine and an acyl chloride because they knew that this reaction, the standard way of making an amide, had a very good chance of success. They chose to disconnect the C–N bond because this disconnection corresponds to a reliable reaction in a way that no other possible disconnection of this molecule does.

Now that you've seen the principle of retrosynthetic analysis at work, you should be able to suggest a reasonable disconnection of this compound, which is known as daminozide.

You probably spotted immediately that daminozide is again an amide, so the best disconnection is the C–N bond, which could take us back to acyl chloride and dimethylhydrazine. This time we've written 'C–N amide' above the retrosynthetic arrow as a reminder of why we've made the disconnection and we advise you to follow this practice.

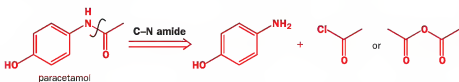


Now, in fact, there is a problem with this acyl chloride—it would be unstable as it can cyclize to an anhydride. But this poses no problem for the synthesis of daminozide—we could just use the anhydride instead, since the reaction should be just as reliable. A better retrosynthesis therefore gives the anhydride and indeed this is how daminozide is made.



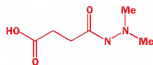
Synthons are idealized reagents

In the synthesis of daminozide an anhydride is used out of necessity rather than out of choice, but it often turns out that there are several alternative reagents all corresponding to the same disconnection. Paracetamol, for example, is an amide that can be disconnected either to amine + acyl chloride or to amine + anhydride.



Which reagent is best can often only be determined by experimentation—commercially, paracetamol is made from *para*-aminophenol and acetic anhydride largely because the by-product, acetic acid, is easier to handle than HCl. In a retrosynthetic analysis, we don't really want to be bothered by this sort of decision, which is best made later, so it's useful to have a single way of representing the key attributes of alternative reagents. We can depict both anhydride and acyl chloride in this scheme as an 'idealized reagent'—an electrophilic acetyl group MeCO^+ .

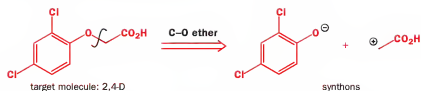
We call such idealized reagents synthons. Synthons are fragments of molecules with an associated polarity (represented by a '+' or '−') which stand for the reagents we are going to use in the forward synthesis. They are not themselves reagents, though they may occasionally turn out to be intermediates along the reaction pathway. By disconnecting bonds to synthons rather than to actual reagents we can indicate the polarity of the bond-forming reaction we are going to use without having to specify details of the reagents.



■ Daminozide is an agrochemical used to stunt the growth of chrysanthemums and dwarf fruit trees artificially.

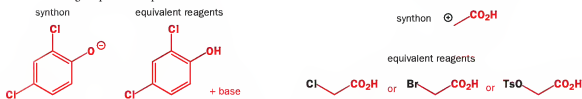
▶ You will find that you learn much more and much faster if you try to do the retrosynthetic analyses in this chapter as you read it, before looking at the suggested solutions. Use a piece of paper to cover up the rest of the page as you read, and write some ideas down on another piece of paper. Don't just say 'oh I can do that' and move on—you'll miss out on the chance of teaching yourself a lot of chemistry. Don't waste the opportunity! Next time you read this chapter you'll have your memory as an aid—and retrosynthetic analysis isn't about remembering; it's about deducing. Another important thing about retrosynthetic analysis is that there is rarely one single 'right' answer, so even if your suggestions don't match up with ours, don't be discouraged. Aim to learn from the points where your attempts differ from our suggestions.



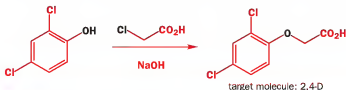


We can apply these ideas to the synthesis of the herbicide 2,4-D (2,4-dichlorophenoxyacetic acid). The most reasonable disconnection of an ether is the C–O bond because we know that ethers can be made from alkyl halides by substitution with an alkoxide anion. We don't at this stage need to decide exactly which alkyl halide or alkoxide to use, so we just write the synthons.

Once the retrosynthetic analysis is done, we can go back and use our knowledge of chemistry to think of reagents corresponding to these synthons. Here, for example, we should certainly choose the anion of the phenol as the nucleophile and some functionalized acetic acid molecule with a leaving group in the α position.



We can then write out a suggested synthesis in full from start to finish. It isn't reasonable to try to predict exact conditions for a reaction: to do that you would need to conduct a thorough search of the chemical literature and do some experiments. However, all of the syntheses in this chapter are real examples and we shall often give full details of conditions to help you become familiar with them.



● Some definitions of terms used in synthesis

- | | |
|---|---|
| • target molecule (or TM) | the molecule to be synthesized |
| • retrosynthetic analysis or retrosynthesis | the process of mentally breaking down a molecule into starting materials |
| • retrosynthetic arrow | an open-ended arrow, \Rightarrow , used to indicate the reverse of a synthetic reaction |
| • disconnection | an imaginary bond cleavage, corresponding to the reverse of a real reaction |
| • synthon | idealized fragments resulting from a disconnection. <i>Synthons</i> need to be replaced by <i>reagents</i> in a suggested synthesis |
| • reagent | a real chemical compound used as the equivalent of a synthon |

Choosing a disconnection

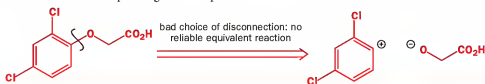
The hardest task in designing a retrosynthetic analysis is spotting where to make the disconnections. We shall offer some guidelines to help you, but the best way to learn is through experience and practice. The overall aim of retrosynthetic analysis is to get back to starting materials that are available from chemical suppliers, and to do this as efficiently as possible.

● Guideline 1

Disconnections must correspond to known, reliable reactions

We have already mentioned that disconnections must correspond to known reliable reactions and it's the most important thing to bear in mind when working out a retrosynthesis. When we disconnected the ether 2,4-D we chose to disconnect next to the oxygen atom because we know about the synthesis of ethers. We chose *not* to disconnect on the aryl side of the oxygen atom because we know of no reliable reaction corresponding to nucleophilic attack of an alcohol on an unactivated aromatic ring.

■ We talked about cases where nucleophilic aromatic substitution is possible in Chapter 23.



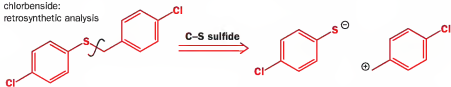
● Guideline 2

For compounds consisting of two parts joined by a heteroatom, disconnect next to the heteroatom

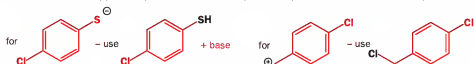
In all the retrosynthetic analyses you've seen so far there is a heteroatom (N or O) joining the rest of the molecule together, and in each case we made the disconnection next to that N or O. This guideline works for esters, amides, ethers, amines, acetals, sulfides, and so on, because these compounds are often made by a substitution reaction.

Chlorbenside is used to kill ticks and mites. Using Guideline 2 we can suggest a disconnection next to the sulfur atom; using Guideline 1 we know that we must disconnect on the alkyl and not on the aryl side.

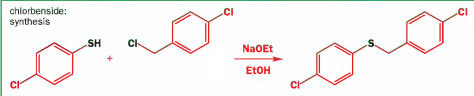
chlorbenside:
retrosynthetic analysis



We can now suggest reagents corresponding to the synthons, and propose a synthetic scheme.



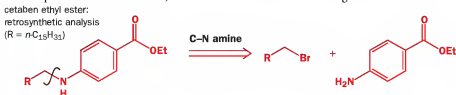
chlorbenside:
synthesis



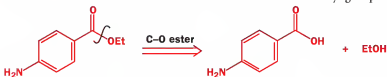
► You shouldn't have expected to predict that sodium ethoxide would be the base used for this reaction, but you should have been aware that a base is needed, and have had some idea of the base strength required to deprotonate a thiol.

▶ You don't always need to write out the synthons first—here the reagents are simple so we just write those instead.

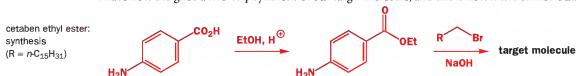
The next example is the ethyl ester of, and precursor to, cetaben, a drug that can be used to lower blood lipid levels. It is an amine, so we disconnect next to the nitrogen atom.



The alkyl bromide is available but we shall need to make the aromatic amino-ester and the best disconnection for an ester is the C–O bond between the carbonyl group and the esterifying group.

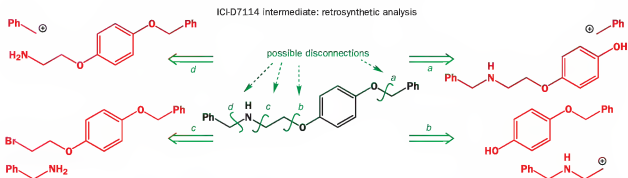


We have now designed a two-step synthesis of our target molecule, and this is how it was carried out.



Multiple step syntheses: avoid chemoselectivity problems

This compound was an intermediate in the synthesis of the potential anti-obesity drug ICI-D7114 you met at the beginning of the chapter. You can spot that, with two ethers and an amine functional group, it requires several disconnections to take it back to simple compounds. The question is which do we do first? One way to solve the problem is to write down all the possibilities and see which looks best. Here there are four reasonable disconnections: one at each of the ether groups (*a* and *b*) or on either side of the amine (*c* and *d*).



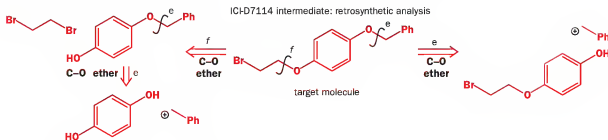
Both (*a*) and (*b*) pose problems of chemoselectivity as it would be hard to alkylate the phenol in the presence of the basic nitrogen atom. Between (*c*) and (*d*), (*c*) appears to be the better choice because the next disconnection after (*d*) will have to be an alkylation of O in the presence of an NH_2 group. To avoid chemoselectivity problems like this, we want to try and *introduce reactive groups late in the synthesis*. In terms of retrosynthetic analysis, then, we can formulate another guideline.

■ We talked about this type of thing in Chapter 24.

● Guideline 3

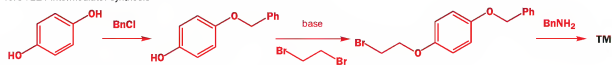
Consider alternative disconnections and choose routes that avoid chemoselectivity problems—often this means disconnecting reactive groups late

This guideline helps us in the next retrosynthetic step for the ICI-D7114 intermediate. Disconnection (c) gave us a compound with two ethers that might be disconnected further by disconnection (e) or (f).



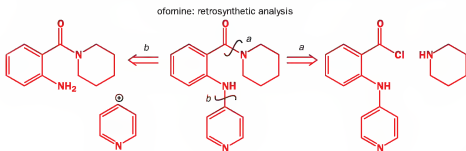
Disconnection (e) requires alkylation of a compound that is itself an alkylating agent. Disconnection (f) is much more satisfactory, and leads to a compound that is easily disconnected to 4-hydroxyphenol (*para*-cresol) and 1,2-dibromethane. Using Guideline 3, we can say that it's best to disconnect the bromoethyl group (f) before the benzyl group because the bromoethyl group is more reactive and more likely to cause problems of chemoselectivity.

ICI-D7114 intermediate: synthesis



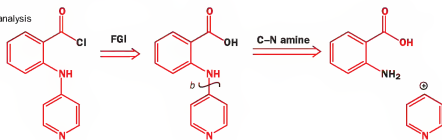
Functional group interconversion

The antihypertensive drug ofornine contains an amide and an amine functional group, and we need to decide which to disconnect first. If we disconnect the secondary amine first (b), we will have chemoselectivity problems constructing the amide in the presence of the resulting NH_2 group.



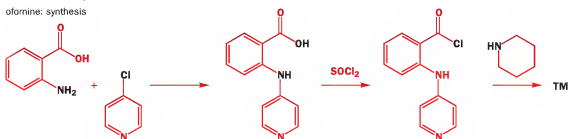
Yet disconnection (a), on the face of it, seems to pose an even greater problem because we now have to construct an amine in the presence of an acyl chloride! However, we shall want to make the acyl chloride from the carboxylic acid, which can then easily be disconnected to 2-aminobenzoic acid (anthranilic acid) and 4-chloropyridine.

ofornine:
retrosynthetic analysis



■ We discussed nucleophilic substitutions on electron-poor aromatic rings like this in Chapter 23 and there is more detail on chloropyridines in Chapter 43.

The retrosynthetic transformation of an acyl chloride to a carboxylic acid is not really a disconnection because nothing is being disconnected. We call it instead a **functional group interconversion**, or FGI, as written above the retrosynthetic arrow. Functional group interconversions often aid disconnections because the sort of reactive functional groups (acyl chlorides, alkyl halides) we want in starting materials are not desirable in compounds to be disconnected because they pose chemoselectivity problems. They are also useful if the target molecule contains functional groups that are not easily disconnected.



By using an appropriate reagent or series of reagents, almost any functional group can be converted into any other. You should already have a fair grasp of reasonable functional group interconversions. They mostly fall into the categories of oxidations, reductions, and substitutions (Chapters 12, 14, 17, and 24).

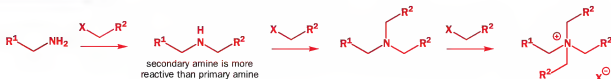
Amine synthesis using functional group interconversions

The synthesis of amines poses a special problem because only in certain cases is the obvious disconnection successful.

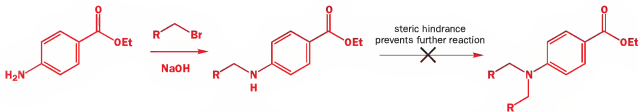


■ We discussed this in Chapters 14 and 24.

The problem is that the product is usually more reactive than the starting material and there is a danger that multiple alkylation will take place.



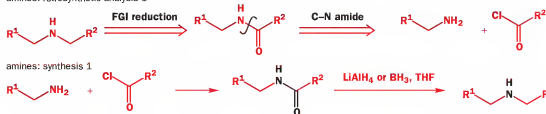
The few successful examples you have seen so far in this chapter have been exceptions, either for steric or electronic reasons, and from now on we advise you to avoid disconnecting an amine in this way. Sometimes further alkylation is made unfavourable by the increased steric hindrance that would result; this is probably the case for the cetaben ethyl ester we made by this reaction.



If the alkylating agent contains an inductive electron-withdrawing group, the product may be less reactive than the starting material—benzylamine was only alkylated once by the alkyl bromide in the synthesis of ICI-D7114 on p. 000 because of the electron-withdrawing effect of the aryloxy group.

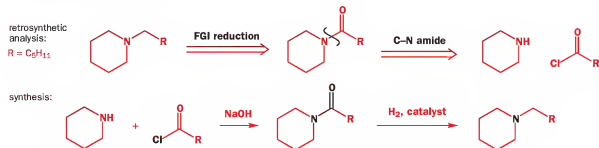
What are the alternatives? There are two main ones, and both involve functional group interconversion, with the reactive amine being converted to a less reactive derivative before disconnection. The first solution is to convert the amine to an amide and then disconnect that. The reduction of amide to amine is quite reliable, so the FGI is a reasonable one.

amines: retrosynthetic analysis 1



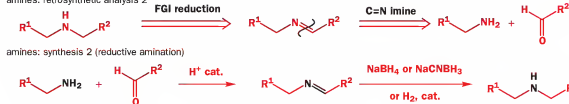
Notice that we write 'FGI reduction' above the arrow because we are talking about the *forward* reaction we are going to do at this step.

This approach was used in a synthesis of this amine, though in this case catalytic hydrogenation was used to reduce the amide.

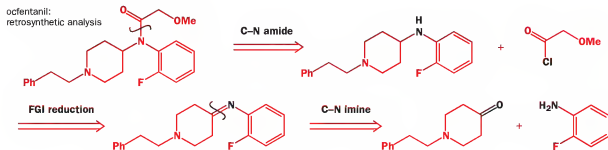


The second alternative is to convert to an imine, which can be disconnected to amine plus carbonyl compound. This approach is known as reductive amination, and we discussed it in detail in Chapter 14.

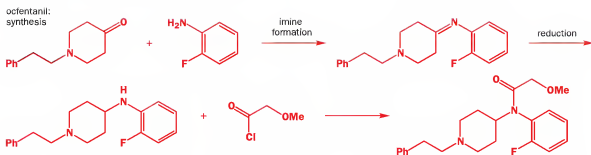
amines: retrosynthetic analysis 2



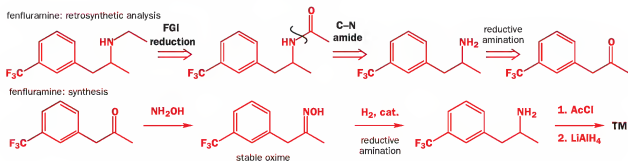
Ocfentanil is an opioid painkiller that lacks the addictive properties of morphine. Disconnection of the amide gives a secondary amine that we can convert to an imine for disconnection to a ketone plus 2-fluoro aniline.



The synthesis is straightforward: a reductive amination followed by acylation of the only remaining NH group. The tertiary amine in the left-hand ring interferes with neither of these reactions.

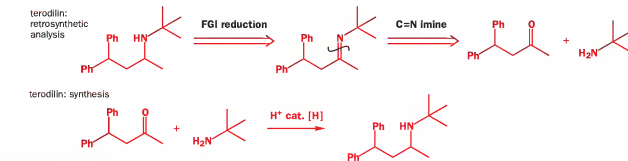


There are several conceivable routes to the neuroactive drug fenfluramine—one analysis, which uses both the amide and the imine FGI methods, is shown below and this was the route used to make the drug. Notice that the oxime was used instead of the imine. *N*-unsubstituted imines are very unstable, and the much more stable, indeed isolable oxime serves the same purpose. Oximes are generally reduced with LiAlH_4 .



You should now be able to suggest a plausible analysis of the secondary amine terodilin. This is the structure; write down a retrosynthetic analysis and suggested synthesis before looking at the actual synthesis below.

You should find yourself quite restricted in choice: the amide route clearly works only if there is a CH_2 group next to the nitrogen (this comes from the $\text{C}=\text{O}$ reduction), so we have to use an imine.

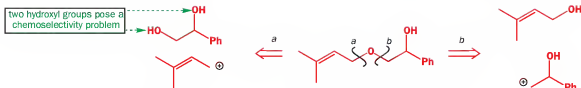


See Chapter 24 for more on this.

In the synthesis of terodilin, it was not necessary to isolate the imine—reduction of imines is faster than reduction of ketones, so formation of the imine in the presence of a mild reducing agent (usually NaCNBH_3 or catalytic hydrogenation) can give the amine directly.

Two-group disconnections are better than one

This compound was needed for some research into the mechanisms of rearrangements. We can disconnect on either side of the ether oxygen atom, but (b) is much better because (a) does not correspond to a reliable reaction: it might be hard to control selective alkylation of the primary hydroxyl group in the presence of the secondary one.



You might think that the best reagent to use as the equivalent of the synthon:

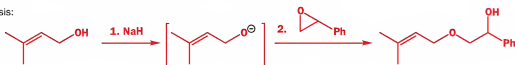


Be more ingenious! A much better solution is to use an epoxide



Nucleophile attack on the less hindered terminal carbon atom of the epoxide gives us the type of compound we want, and this was how the target molecule was made.

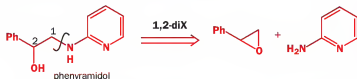
synthesis:



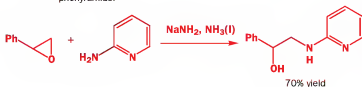
In using the epoxide we have gone one step beyond all the disconnections we have talked about so far, because we have *used one functional group to help disconnect another*—in other words, we noticed the alcohol adjacent to the ether we wanted to disconnect, and managed to involve them both in the disconnection. Such disconnections are known as **two-group disconnections**, and you should always be on the look-out for opportunities of using them because they are an efficient way of getting back to simple starting materials. We call this epoxide disconnection a 1,2-disconnection because the two functional groups in the two-group disconnection are in a 1,2-relationship.

Drug molecules often have 1,2-related functional groups: 2-amino alcohols form one important class. Phenylramidol, for example, is a muscle relaxant. A simple two-group disconnection takes it straight back to 2-amino pyridine and styrene oxide.

phenylramidol:
retrosynthetic analysis



phenylramidol:
synthesis

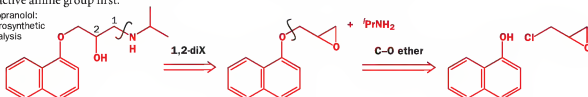


Notice that we have written '1,2-diX' above the arrow to show that it's a two-group ('diX') disconnection—we've also numbered the carbon atoms in the starting material to show the 1,2-relationship. It may seem trivial in such a simple example, but it's a useful part of the process of writing retrosynthetic analyses because it helps you to spot opportunities for making two-group disconnections.

Propranolol is one of the top heart drugs

The Zeneca drug propranolol is a beta-blocker that reduces blood pressure and is one of the top drugs worldwide. It has two 1,2-relationships in its structure but it is best to disconnect the more reactive amine group first.

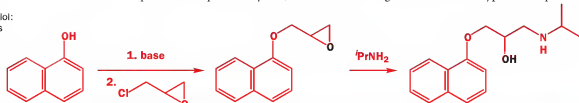
propranolol:
retrosynthetic analysis



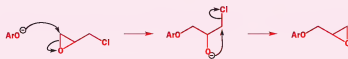
The observant among you may now be questioning why this synthesis is successful—after all, we have made a secondary amine by alkylating a primary one with an epoxide—exactly the sort of thing we advised against on p. 000. Alkylations with epoxides usually stop after the first step because the inductively electron-withdrawing hydroxyl group in the product makes it less nucleophilic than the starting material. In the synthesis of ICI-D7114 on p. 000, it's this same effect that prevents the amine being multiply alkylated.

The second disconnection can't make use of an epoxide, but a simple ether disconnection takes us back to 1-naphthol and epichlorohydrin, a common starting material for this type of compound.

propanolol:
synthesis



Epichlorohydrin is a useful starting material for 1,2,3-substituted compounds. The epoxide is more electrophilic than the C-Cl bond, and the mechanism of the first step of the synthesis is surprising.

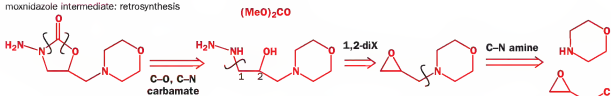


How would you verify this experimentally? Think about what would happen if the epichlorohydrin were enantiomerically pure.

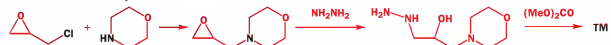
Moxnidazole can be made with epichlorohydrin

Moxnidazole is an antiparasitic drug, and our next target molecule is an important intermediate in its synthesis. The obvious first disconnection is of the carbamate group, revealing two 1,2 relationships. A 1,2-diX disconnection gives an epoxide that can be made by alkylation of morpholine with epichlorohydrin.

moxnidazole intermediate: retrosynthesis



moxnidazole intermediate: synthesis



At the carbonyl oxidation level another synthon is needed for 1,2-diX disconnections

Just as epoxides are useful reagents for this synthon:



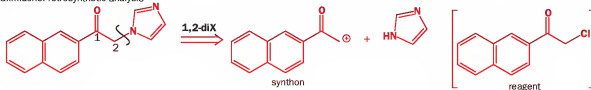
α halocarbonyl compounds are useful reagents for the carbonyl equivalent:



We can consider disconnection to this synthon to be a two-group disconnection because the α halocarbonyl equivalents are easily made by halogenation of a ketone, ester, or carboxylic acid (see Chapter 21) and the carbonyl group adjacent to the halide makes them extremely reactive electrophiles (Chapter 17).

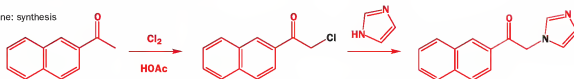
Nafimidone is an anticonvulsant drug with an obvious two-group disconnection of this type.

nafimidone: retrosynthetic analysis



The α chloroketone is simply made by chlorination, and substitution is rapid and efficient even with the weakly basic (Chapter 8) heterocyclic amine.

naftimidone: synthesis



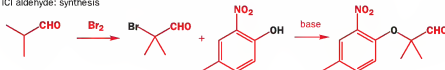
The aldehyde below was needed by ICI when they were developing a thromboxane antagonist. Two-group disconnection gives a 2-halo-aldehyde that can be made from isobutyraldehyde.

ICI aldehyde: retrosynthetic analysis



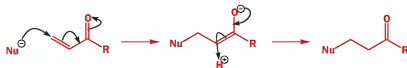
The synthesis requires a normal bromination of a carbonyl compound in acid solution but the next step is a most unusual S_N2 reaction at a *tertiary* centre. This happens because of the activation by the aldehyde group (Chapter 17) and is further evidence that the functional groups must be thought of as working together in this type of synthesis.

ICI aldehyde: synthesis

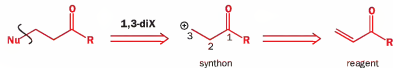


1,3-Disconnections

In Chapter 10 you saw how α,β -unsaturated carbonyl compounds undergo conjugate additions—reactions like this.

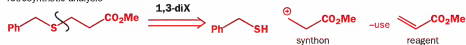


Two-group 1,3-disconnections are therefore possible because they correspond to this forward reaction. These Michael acceptors have an electrophilic site two atoms away from the carbonyl group, and are therefore the reagents corresponding to this synthon.



This type of reaction is available only when the alkene is conjugated to an electron-withdrawing group—usually carbonyl (Chapter 10) but it can be nitro, cyanide, etc. (Chapter 23). This disconnection is available only at this oxidation level unlike the last. We can do a two-group 1,3-disconnection on this sulfide, for example.

retrosynthetic analysis



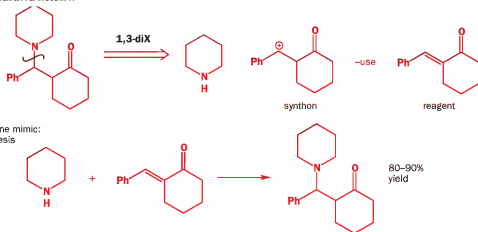
synthesis



■ We shall discuss ways of disconnecting this starting material, and other α,β -unsaturated carbonyl compounds, later in the chapter.

▶ Don't be tempted to try using β haloketones as equivalents for this synthon! They are hard to make and highly unstable and they undergo rapid E1cB elimination (see Chapter 19).

atropine mimic:
retrosynthetic analysis



To summarize...

Before we leave C–X disconnections and go on to look at C–C disconnections we should just review some important points. We suggested three guidelines for choosing disconnections and now that you have met the principle of two-group disconnections, we can add a fourth:

● Guidelines for good disconnections

1. Disconnections must correspond to known, reliable reactions
2. For compounds consisting of two parts joined by a heteroatom, disconnect next to the heteroatom
3. Consider alternative disconnections and choose routes that avoid chemoselectivity problems—often this means disconnecting reactive groups first
4. Use two-group disconnections wherever possible

Two-group disconnections reduce the complexity of a target molecule more efficiently than one-group disconnections, and you should always be on the look-out for them. You will meet more two-group disconnections in the next section, which deals with how to disconnect C–C bonds.

C–C disconnections

The disconnections we have made so far have all been of C–O, C–N, or C–S bonds, but, of course, the most important reactions in organic synthesis are those that form C–C bonds. We can analyse C–C disconnections in much the same way as we've analysed C–X disconnections. Consider, for example, how you might make this simple compound, which is an intermediate in the synthesis of a carnation perfume.



The only functional group is the triple bond, and we shall want to use the chemistry of alkynes to show us where to disconnect. You know that alkylation of alkynes is a reliable reaction, so a sensible disconnection is next to the triple bond.

camomile perfume intermediate: retrosynthetic analysis



camomile perfume intermediate: synthesis



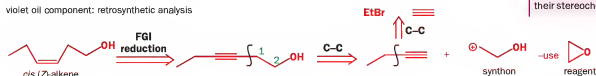
Alkynes are particularly valuable as synthetic intermediates because they can be reduced either to *cis* or to *trans* double bonds.



It's often a good idea to start retrosynthetic analysis of target molecules containing isolated double bonds by considering FGI to the alkyne because C–C disconnections can then become quite easy.

This *cis*-alkene is a component of violet oil, and is an intermediate in the synthesis of a violet oil component. FGI to the alkyne reveals two further disconnections that make use of alkyne alkylations. The reagent we need for the first of these is, of course, the epoxide as there is a 1,2-relationship between the OH group and the alkyne.

violet oil component: retrosynthetic analysis

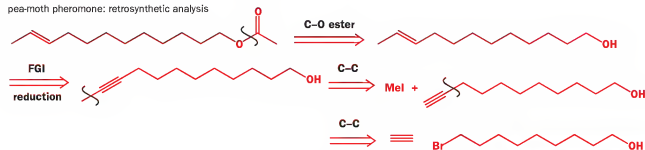


violet oil component: synthesis



The next example is the pheromone of the pea-moth, and can be used to trap the insects (see the introduction to Chapter 24). After disconnecting the ester, FGI on the *trans* double bond gives an alkyne.

pea-moth pheromone: retrosynthetic analysis



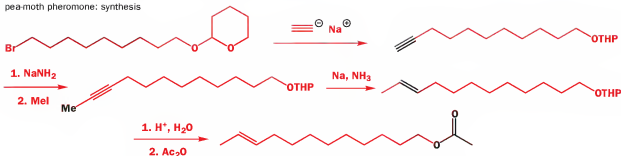
Disconnection on either side of the alkyne leads us back to a bromo-alcohol alkylating agent. In the synthesis of the pheromone, it turned out to be best if the hydroxyl group was protected as its THP ether. You should be able to think of other alkylation-type reactions that you have met that proceed reliably and therefore provide a good basis for a disconnection—the alkylation of enolates of esters or ketones, for example (Chapter 26).

You met these reductions in Chapter 24, and we will talk about them again in the context of double bond synthesis in Chapter 31.

There are, of course, many other ways of disconnecting double bonds: you are about to meet an important disconnection of double bonds conjugated with carbonyl groups. Chapter 31 is devoted to the alternative methods available for making double bonds and controlling their stereochemistry.

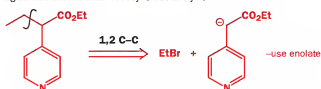
Protecting groups were discussed in detail in Chapter 24.

pea-moth pheromone: synthesis

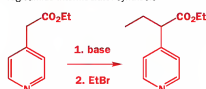


This next ester was needed for a synthesis of the sedative rogitimide (see later for the full synthesis). The ethyl group is disconnected because it can be readily introduced by alkylation of the ester enolate.

rogitimide intermediate: retrosynthetic analysis



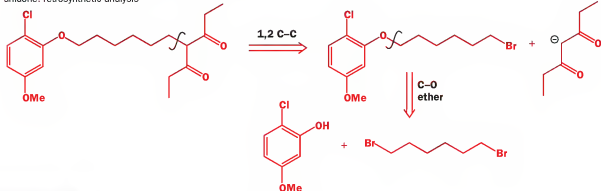
rogitimide intermediate: synthesis



We have labelled the disconnection '1,2 C-C' because the new C-C bond is forming two atoms away from the carbonyl group. To spot disconnections of this sort, you need to look for alkyl groups in this 2-position.

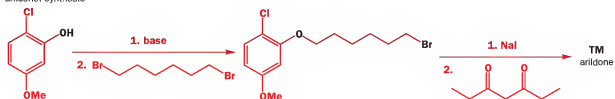
Aridone is a drug that prevents polio and herpes simplex viruses from 'unwrapping' their DNA, and renders them harmless. It has just the structural characteristic you should be looking for: a branch next to a carbonyl group.

aridone: retrosynthetic analysis



Look back to Chapter 26 if you don't understand why.

aridone: synthesis

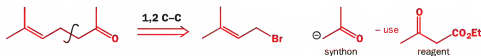


We introduced the chemistry of malonate esters in Chapters 21 and 26 as a useful way of controlling the enolization of carbonyl compounds. Alkylation followed by decarboxylation means that we can treat acetoacetate and malonate esters as equivalent for these syntheses.

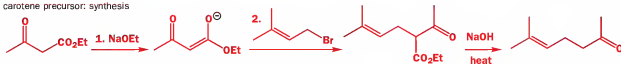


This unsaturated ketone is an important industrial precursor to β -carotene, vitamin A, and other similar molecules. Disconnection using the carbonyl group gives a synthon for which a good reagent will be acetoacetate.

carotene precursor: retrosynthetic analysis

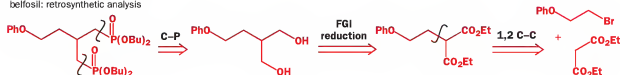


carotene precursor: synthesis



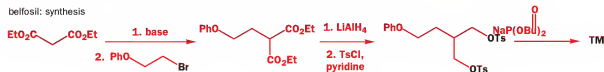
This organophosphorus compound, belfosil, is a Ca^{2+} channel blocker. You haven't met many phosphorus compounds yet, but you should be able to reason that a good disconnection will be the C–P bond by analogy with the sulfides you met earlier in the chapter. We could use bromide as a leaving group, but alkyl bromides are inconvenient to disconnect further, so we go back to the more versatile diol—in the forward synthesis we shall need a way of making the OH groups into good leaving groups. There is still no obvious disconnection of the diol, but FGI to the ester oxidation level reveals a malonate derivative.

belfosil: retrosynthetic analysis



In the synthesis, the diol was converted to the bis-tosylate (see Chapter 17 if you've forgotten about tosylates and mesylates) and reacted with a phosphorus nucleophile.

belfosil: synthesis



Notice how we disconnected the phosphorus-based functional groups straight back to alcohols in the retrosynthetic analysis, and not, say, to alkyl halides. Oxygen-based functional groups (alcohols, aldehydes, ketones, esters, and acids) have one important property in common—versatility. They are easily converted into each other by oxidation and reduction, and into other groups by substitution. What is more, many of the C–C disconnections you will meet correspond to reactions of oxygen-based groups, and particularly carbonyl groups. Faced with an unusual functional group in a target molecule the best thing to do is convert it to an oxygen-based group at the same oxidation level—it usually makes subsequent C–C disconnections simpler. So we add a new guideline.

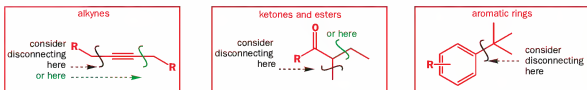
● Guideline 5

Convert to oxygen-based functional groups to facilitate C–C disconnections

Having read Chapter 27, you should be able to suggest why the enolate of acetone itself would not be a good choice in this reaction.

Looking for 1,2 C–C disconnections

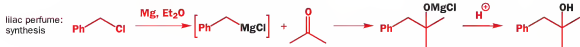
In each of the cases you have met so far, we have used a functional group present in the molecule to help us to disconnect the C–C bond using a 1,2 C–C disconnection. You can look for 1,2 C–C disconnections in alkynes, carbonyl compounds, and alkylated aromatic rings. And, if the target isn't a carbonyl compound, consider what would be possible if functional groups such as hydroxyl groups were converted to carbonyl groups (just as we did with belfosdil).



All of these disconnections relied on the reaction of a carbon electrophile with a nucleophilic functional group. The alternative, reaction of a carbon nucleophile (such as a Grignard reagent) with an electrophilic functional group, allows us to do C–C disconnections on alcohols. For example, this compound, which has a fragrance reminiscent of lilac, is a useful perfume for use in soap because (unlike many other perfumes that are aldehydes or ketones) it is stable to alkali.

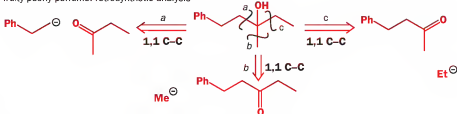


We look to the one functional group, the hydroxyl, to tell us where to disconnect, and disconnection next to the OH group gives two synthons for which sensible reagents are a Grignard reagent and acetone. The perfume is made from benzyl chloride and acetone in this way. Notice that we label these disconnections 1,1 C–C because the bond being disconnected is attached to the same carbon atom as the hydroxyl functional group.

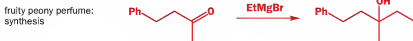


This similar alcohol has a 'peony-like fruity odour' and could be disconnected in three ways.

fruity peony perfume: retrosynthetic analysis



Disconnection (c) leads back to a ketone, which is cheaply made starting from acetone and benzaldehyde, and this was the route that was chosen for the synthesis.

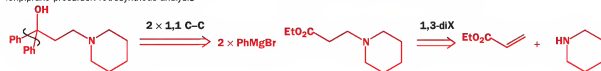


The synthesis of this starting material involves an aldol reaction between acetone and benzaldehyde of the sort discussed in Chapter 27 followed by hydrogenation of the double bond.

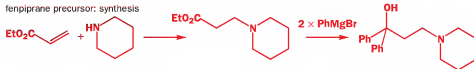
Double disconnections can be a short cut

Tertiary alcohols with two identical groups next to the hydroxyl group are often made by attack of two equivalents of a Grignard reagent on an ester. The synthesis of the antihistamine compound fenpropirone provides an example: the tertiary alcohol is a precursor to the drug and can be disconnected to ester + Grignard reagent because of the two Ph groups. The ester required has a 1,3 functional group relationship, and can be disconnected to amine plus Michael acceptor.

fenpropirone precursor: retrosynthetic analysis



fenpropirone precursor: synthesis

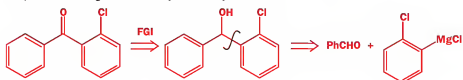


The fact that Grignard reagents add twice to esters means that disconnection of a *ketone* in this way is often not reliable. We talked about a few ways of doing this type of reaction in Chapter 12.

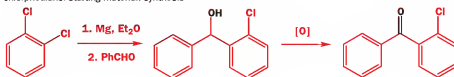


An alternative is to first convert to the alcohol oxidation level, then disconnect. This was the method chosen for this starting material for the synthesis of chlorphedianol.

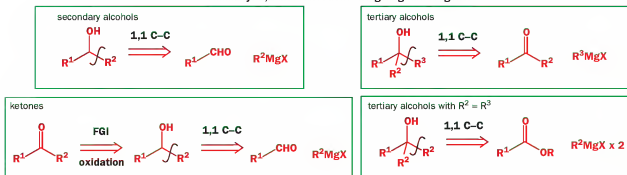
chlorphedianol starting material: retrosynthetic analysis



chlorphedianol starting material: synthesis



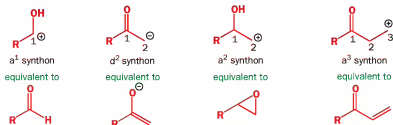
Summary: 1,1 disconnections using Grignard reagents



Donor and acceptor synthons

You've now met a variety of synthons and it's useful to be able to classify them as donor or acceptor synthons. We call a negatively polarized synthon a donor synthon and give it the symbol 'd'. Positively polarized synthons are called acceptor synthons and are given the symbol 'a'.

We can classify the synthons further according to where the functional group is in relation to the reactive site. The first synthon in the diagram below, which corresponds to an aldehyde, we call an a^1 synthon, because it is an acceptor that carries a functional group on the same carbon as its reactive centre. The second is a d^2 synthon because it is a donor whose reacting site is in the 2-position relative to the carbonyl group. Earlier you met two other types of synthon, corresponding to epoxide and Michael acceptor, and we can now classify these as a^2 and a^3 synthons.



This terminology is useful because it reduces synthons to the bare essentials: what polarity they are and where the polarity is sited. The actual functional group they carry is, as you now appreciate, less important because FGI will usually allow us to turn one FG into another.

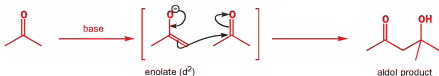
● Synthons are classified as a (acceptor) or d (donor)

- A number shows the position of the acceptor or donor site relative to a functional group
- An a^1 synthon is a carbonyl compound and a d^2 synthon an enolate

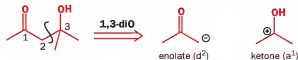
Two-group C–C disconnections

1,3-Difunctionalized compounds

It's not only Grignard reagents that will react with aldehydes or ketones to make alcohols: enolates will too—we spent Chapters 27 and 28 discussing this reaction, the aldol reaction, its variants, and ways to control it.

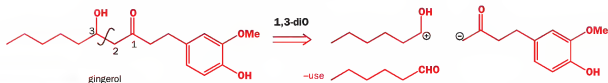


The aldol reaction is extremely important in organic synthesis because it makes compounds with two functional groups in a 1,3-relationship. Whenever you spot this 1,3-relationship in a target molecule—think aldol! In disconnection terms we can represent it like this.



We call this disconnection a two-group C–C disconnection, because we are using the OH and the C=O groups together to guide our disconnection. The disconnection gives us a d^2 synthon for which we shall use an enolate equivalent, and an a^1 synthon, for which we shall use an aldehyde or a ketone.

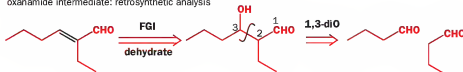
Chapter 27 has many examples and perhaps gingerol is the best. As soon as you see the 1,3-relationship, the disconnection should be obvious.



The elimination is easy because it goes by an E1cB mechanism—see Chapter 18.

The β -hydroxy carbonyl products of aldol reactions are often very easily dehydrated to give α,β -unsaturated carbonyl compounds and, if you spot an α,β -unsaturated carbonyl group in the molecule, you should aim to make it by an aldol reaction. You will first need to do an FGI to the β -hydroxy carbonyl compound, then disconnect as before.

oxanamide intermediate: retrosynthetic analysis



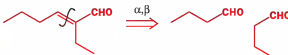
This aldehyde is an intermediate in the synthesis of the tranquilizer oxanamide. Because both components of the aldol reaction are the same, no special precautions need to be taken to prevent side-reactions occurring. In the synthesis, the dehydration happened spontaneously.

oxanamide intermediate: synthesis



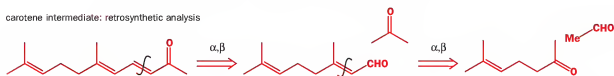
Because this disconnection of unsaturated carbonyl compounds is so common, it's often written using a shorthand expression.

oxanamide intermediate: retrosynthetic analysis



The next compound was needed for an early synthesis of carotene. Again, it's an α,β -unsaturated ketone so we can disconnect using the same ' α,β ' disconnection.

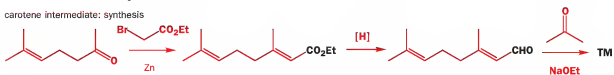
carotene intermediate: retrosynthetic analysis



The aldehyde generated by this first disconnection is also α,β -unsaturated, so we can do another α,β disconnection, back to a ketone whose synthesis we have already discussed (p. 000).

An aldol reaction using the enolate of acetaldehyde and requiring it to react with a ketone is doomed to failure: acetaldehyde itself is far too good an electrophile. In the forward synthesis, therefore, this first step was carried out at the ester oxidation level (using a Reformatsky reaction), and the ester was subsequently converted to the aldehyde by a reduction of the kind discussed in Chapter 24.

carotene intermediate: synthesis

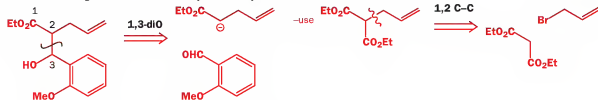


There was no problem with selectivity in the second aldol reaction because the aldehyde is not enolizable. The Reformatsky reaction in this sequence illustrates the fact that, of course, aldol-type

reactions happen at the ester oxidation level as well, and you should equally look to disconnect β -hydroxy or α,β -unsaturated esters, acids, or nitriles in this way. Just remember to look for 1,3-relationships, convert the functional groups to oxygen-based ones, and disconnect them to d^2 plus a^1 synthons.

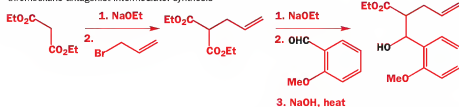
The next compound was needed by ICI when chemists there were developing a thromboxane antagonist to inhibit blood clot formation. You can immediately spot the 1,3-relationship between the ester and the hydroxyl group, so 1,3-diO disconnection is called for.

thromboxane antagonist intermediate: retrosynthetic analysis



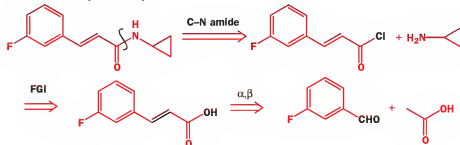
A good equivalent for the 'ester enolate' d^2 synthon is a β -dicarbonyl compound, because it can easily be disconnected to diethyl malonate and an alkylating agent.

thromboxane antagonist intermediate: synthesis



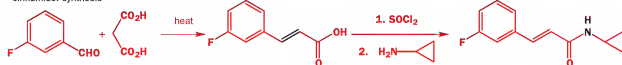
This unsaturated amide is known as cinflumide and is a muscle relaxant. Disconnection of the amide gives an acid chloride that we can make by FGI from the acid. You should then spot the α,β -unsaturated carbonyl disconnection, a masked 1,3-diO disconnection, back to *m*-fluorobenzaldehyde.

cinflumide: retrosynthetic analysis



Again, the forward reaction was best done using malonate chemistry but the variant with malonic acid was used. The cyclopropyl amine unit (here as an amide) is present in many biologically active compounds and the free amine is available.

cinflumide: synthesis

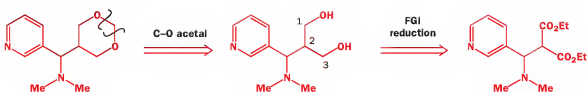


Functional group relationships may be concealed by protection

The analgesic doxipicomine is a more difficult problem than those you have seen so far. At first sight it has no useful disconnections especially as there are no carbonyl groups. However, removal of the acetal reveals a 1,3-diol that could be formed by reduction of a much more promising diester.

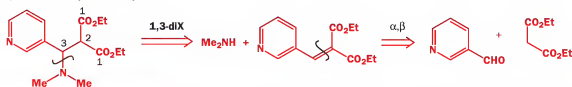
■ If you don't understand what we are saying here, you must go back and read Chapter 27 on selectivity in the aldol reaction.

doxipicoline: retrosynthetic analysis I



The diester has a 1,3-diCO relationship and could be disconnected but we have in mind using malonate so we would rather disconnect the alternative 3-amino carbonyl compound (the Me_2N group has a 1,3-relationship with both ester groups) by a 1,3-diX disconnection giving an unsaturated ester. This α,β -unsaturated ester disconnects nicely to a heterocyclic aldehyde and diethyl malonate.

doxipicoline: retrosynthetic analysis II



It is interesting to note that acetals, usually employed for protection, can be useful in their own right as in this drug.

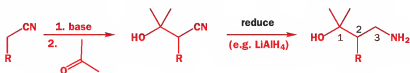
The synthesis is shorter than the retrosynthetic analysis and involves only three steps. Good retrosynthetic analysis, using two-group disconnections, should lead to short syntheses.

doxipicoline: synthesis

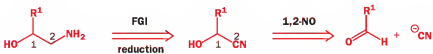
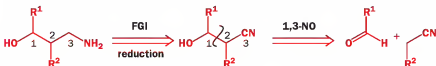


Aldol-style disconnections with N and O in a 1,3-relationship: I

Another important class of compounds that undergo aldol-type additions to aldehydes and ketones is nitriles. Because nitriles can be reduced to amines, this reaction provides another useful route to 3-amino-alcohols.



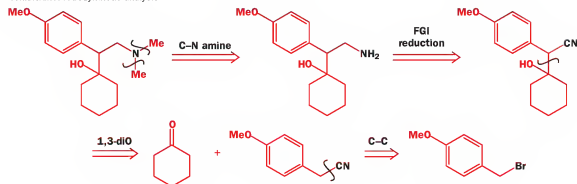
This reaction, coupled with the reduction of cyanohydrins (Chapter 6), means that compounds with either a 1,3- or a 1,2-relationship between N and O can be made from cyanides.



Venlafaxine is an antidepressant and, like many neuroactive agents, it is an amino-alcohol. In this case, the two functional groups are 1,3-related, so we aim to use a 1,3-diO disconnection. Usually,

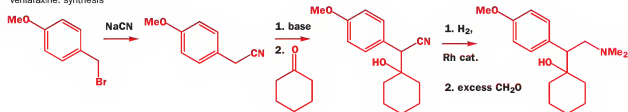
you would convert the amine to an alcohol to simplify the disconnection, but by spotting the opportunity for using a nitrile you can avoid the need for this extra step. A preliminary removal of the two *N*-Me groups is necessary.

venlafaxine: retrosynthetic analysis



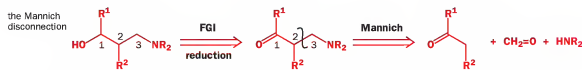
In the forward synthesis, it turned out that the nitrile reduction was best done using hydrogen and a metal (Rh) catalyst. The final methylation of the primary amine had to be done via the imine and iminium ion (see Chapter 24) to prevent further unwanted alkylations. The reagent was an excess of formaldehyde (methanal $\text{CH}_2=\text{O}$). Problem xx offers a chance to try this mechanism.

venlafaxine: synthesis



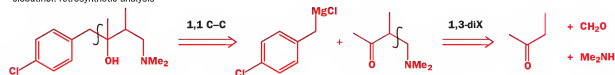
Aldol-style disconnections with N and O in a 1,3-relationship: II—the Mannich reaction

Another important reaction for making amines with a 1,3-relationship to a carbonyl group is the Mannich reaction. You met this in Chapter 27 as a way of doing otherwise unreliable aldol additions to formaldehyde. Because the amine is introduced directly and not by reduction of a nitrile, it can have two alkyl groups from the start. Compare this scheme with the one above using a nitrile group as the source of the amine.

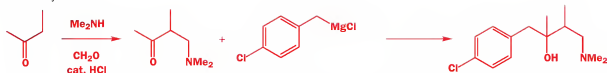


Our example is clobutinol—an antitussive (cough medicine). A preliminary 1,1 C–C disconnection of the tertiary alcohol is necessary to provide a 3-amino ketone that we can make by a Mannich reaction.

clobutinol: retrosynthetic analysis

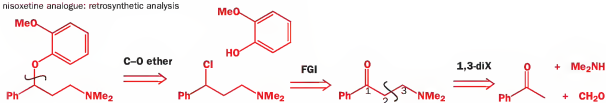


clobutinol: synthesis



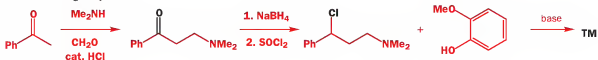
You can immediately spot the 1,3 relationship in this analogue of the antidepressant, nisoxetine, but, unfortunately, it can't be disconnected straight back to an amino-alcohol because that would require nucleophilic substitution on an electron-rich aromatic ring. We have to disconnect the ether on the other side, giving an alkyl chloride.

nisoxetine analogue: retrosynthetic analysis



Using guideline 5 (p. 000) we want to convert the halide to an oxygen-based group, and a sensible solution is to choose the ketone. 1,3-Disconnection of this compound corresponds to a Mannich reaction. This is another case where FGI of the amine to an alcohol is not desirable, because the Mannich reaction will produce the amine directly.

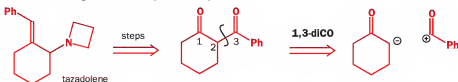
nisoxetine analogue: synthesis



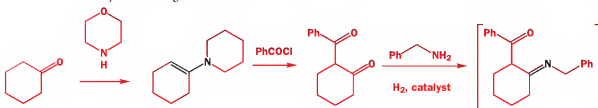
The Claisen ester disconnection: a 1,3-diO relationship needing two carbonyl groups

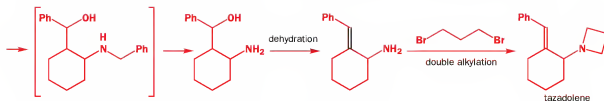
1,3-Diketones can be disconnected in a similar way: this time the disconnection corresponds to a Claisen condensation, but it's still 1,3-diO, and again you need to look out for the 1,3 relationship. The synthons are still d^2 plus a^1 but the a^1 synthon is used at the ester oxidation level. This diketone is the starting material for the synthesis of the antidepressant tazadole. With 1,3-diketones, there's always a choice where to disconnect, and you should be guided by which disconnection (1) corresponds to the most reliable reaction and (2) gives the simplest starting materials. In this case, it's much better to disconnect back to cyclohexanone.

tazadole starting material: retrosynthetic analysis



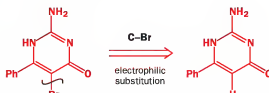
The synthesis is interesting because, after the acylation of the enamine, the amino group is introduced by a clever reductive amination with benzylamine (PhCH_2NH_2) that forms the C-N bond, reduces the ketone, and hydrogenolyses the N-benzyl bond (Chapter 24). Dehydration and double alkylation then give tazadole.





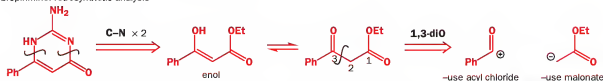
The 1,3-dicarbonyl relationship may not be revealed in the target molecule and C-heteroatom disconnections or FGIs may be needed before the 1,3-diO C-C disconnection. Broprimine is a bromine-containing antiviral and anticancer drug. The bromine atom can be put in last of all by electrophilic bromination.

broprimine: retrosynthetic analysis



Disconnection of two C-N bonds removes a molecule of guanidine and reveals a 1,3-dicarbonyl relationship with a straightforward disconnection.

broprimine: retrosynthetic analysis

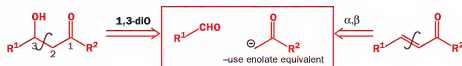


In the event, the 1,3-dicarbonyl was made using malonate chemistry with an unusual twist: the lithium derivative gave C-acylation in good yield. Simply refluxing the product with guanidine formed the heterocycle and bromination gave broprimine.

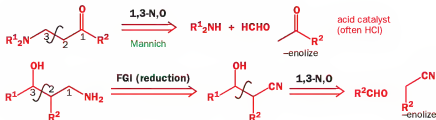
■ Guanidine is the strong delocalized organic base mentioned in Chapter 8.

Summary: 1,3-diO disconnections

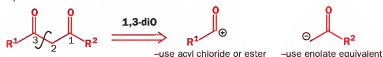
3-hydroxy carbonyls and α,β -unsaturated carbonyls: use the aldol reaction



3-amino ketones and alcohols: use Mannich or nitrile aldol



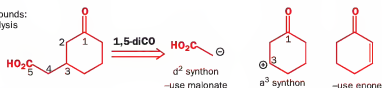
1,3-diketones: use the Claisen condensation



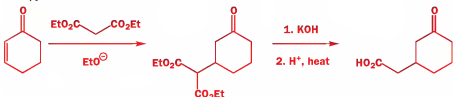
1,5-Related functional groups

This compound has a 1,5 rather than a 1,3 relationship between two carbonyl groups. Disconnection to give an enolate as one reagent therefore requires an a^3 rather than an a^1 synthon: in other words a Michael acceptor.

1,5-dicarbonyl compounds:
retrosynthetic analysis

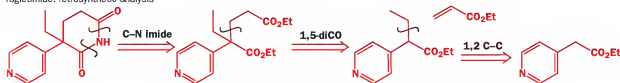


The synthesis will be successful only if (1) the right reagent enolizes and (2) the nucleophile undergoes conjugate (and not direct 1,2-) addition to the unsaturated carbonyl compound (Chapter 29). Malonate derivatives enolize easily *and* do Michael additions and are therefore a good choice for this type of reaction.



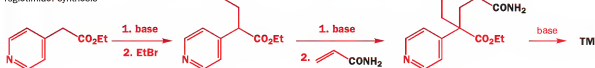
Michael addition of enolates to α,β -unsaturated compounds is a good way of making 1,5-difunctionalized compounds, and you should look for these 1,5-relationships in target molecules with a view to making them in this way. Our example is roglitimide, a sedative that can be disconnected to a 1,5-diester. Further 1,5-diCO disconnection gives a compound we made earlier by ethylation of the ester enolate.

roglitimide: retrosynthetic analysis



■ There are many examples of conjugate addition of enolates in Chapter 29.

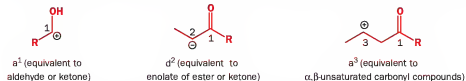
roglitimide: synthesis



The synthesis was most efficient with an unsaturated amide as Michael acceptor.

'Natural reactivity' and 'umpolung'

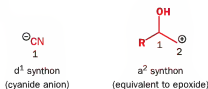
Cast your mind back over the synthons we have used in these two-group C-C disconnections.



Notice that the acceptor synthons have odd numbers; the donor synthon has an even number: donor and acceptor properties alternate along the chain as we move away from a carbonyl group. This 'natural reactivity' of carbonyl compounds explains why we find it easy to discuss ways of making 1,3- and 1,5-difunctionalized compounds, because they arise from $a^1 + d^2$ and from $a^3 + d^2$. Reagents corresponding to synthons like d^1 or a^2 are rarer, and therefore compounds with 1,2- or 1,4- related functional groups require special consideration retrosynthetically.

You have in fact met one example of each of the 'unnatural' synthons with a^2 and d^1 reactivity. Such synthons are given the German name *Umpolung*, meaning 'inverse polarity' because their natural reactivity is reversed, and umpolung reagents are the key to the synthesis of 1,2- and 1,4-difunctionalized compounds.

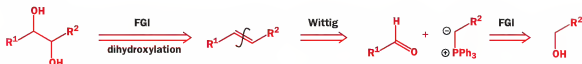
two umpolung reagents



We shall finish this chapter by looking at disconnections of 1,2- and 1,4-difunctionalized compounds because these require us to use reagents with umpolung equivalent to d^1 , d^3 , a^2 , and a^4 synthons. There are very many reagents for these synthons—if you are interested to learn more, consult a specialized book.

1,2-Difunctional compounds

You met ways of making 1,2-difunctionalized compounds when we first talked about two-group disconnections, and we used an epoxide as an a^2 synthon. Epoxides are, of course, also 1,2-functionalized, and in fact this is often the key to making 1,2-functionalized compounds: use something with the 1,2 relationship already in place. You saw lots of examples of this type of strategy earlier in this chapter. Perhaps the simplest approach is electrophilic addition to alkenes. If the alkene is made by a Wittig reaction, the disconnection is (eventually) between the two functionalized carbon atoms in the target molecule. This example shows dihydroxylation as the electrophilic addition but there is also epoxidation, bromination, and bromination in water to give Br and OH as the functional groups.



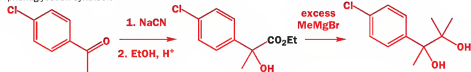
A normal C–C disconnection is also a possibility, but disconnection to the 'natural' a^1 synthon and the umpolung d^1 is necessary. One very useful umpolung reagent is cyanide, and you can see it in action in this synthesis of the tranquillizer phenaglycodol. The tertiary alcohol with two R groups the same should prompt you to think of doing a double Grignard addition to an ester. FGI then reveals the nitrile functional group necessary for a 1,2-diX disconnection to cyanide plus ketone.

phenaglycodol: retrosynthetic analysis



The starting material is obviously available by a Friedel–Crafts acylation of chlorobenzene and the rest of the synthesis follows. Note that the nitrile can be converted directly into the ester with acidic ethanol and that an excess of Grignard reagent is needed because the free OH group destroys some of it.

phenaglycodol: synthesis



1,4-Difunctional compounds

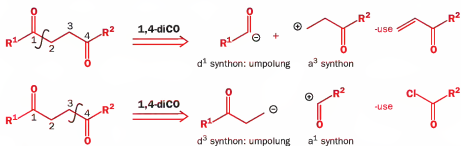
There are more possibilities here and we shall finish this chapter with a brief analysis of them to show you how much of this subject lies beyond what we can do in this book. If we start with a 1,4-dicarbonyl compound we might consider first disconnection of the central bond.



We can use an enolate for one reagent but the other will have to have umpolung. This is not a very serious kind of umpolung as an α -bromo carbonyl compound will do the job nicely if we select our enol(ate) equivalent carefully. In Chapter 26 we suggested enamines for this job. The synthesis becomes:

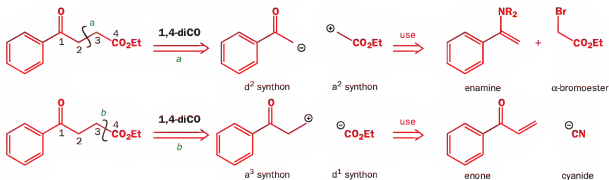


If we attempt the disconnection of one of the other bonds, two possibilities are available because the two fragments are different. We can use either a $d^1 + a^3$ strategy or an $a^1 + d^3$ strategy. In each case we have one natural synthon and one with umpolung.



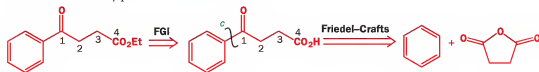
Another approach using the nitro group and the Nef reaction appears at the end of Chapter 29.

These strategies are more difficult to realize with the reagents you have met so far but conjugate addition of a cyanide to an unsaturated carbonyl compound would be an example of the $d^1 + a^3$ strategy. We have included these to try to convince you that there is no escape from umpolung in the synthesis of a 1,4-dicarbonyl compound. If you were making this keto-ester you would have to understand two of the three strategies.



There is one way to avoid umpolung and that is to make the disconnection outside the 1,4 relationship. As it happens, we have already seen this strategy in action (p. 000). It involves a Friedel-Crafts acylation of benzene (Chapter 22) with a cyclic anhydride and leads directly to this

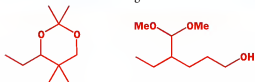
product by quite a short route. This strategy is available only if there happens to be a starting material available to suit any particular case.



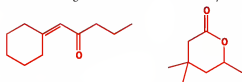
This chapter is meant to give you just the basic ideas of retrosynthetic analysis. They are important because they reinforce the concept that the combination of electrophile and nucleophile is the basis for the understanding of organic reactions. Synthesis and reactions are two sides of the same coin. From now on we shall use the methods introduced in this chapter when we think that they will help you to develop your understanding.

Problems

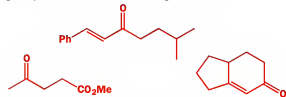
1. Suggest ways to make these two compounds. Show your disconnections and don't forget to number the relationships.



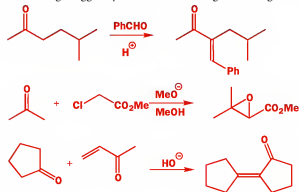
2. Propose syntheses of these two compounds, explaining your choice of reagents and how the necessary selectivity is achieved.



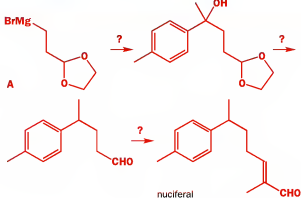
3. The reactions to be discussed in this problem were planned to give syntheses of these three target molecules.



In the event, each reaction gave a different product shown below. What went wrong? Suggest syntheses that would give the target molecules.

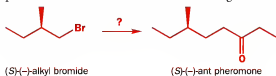


4. The natural product nuciferal was synthesized by the route summarized here.

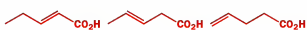


- (a) Suggest a synthesis of the starting material A.
(b) Suggest reagents for each step.
(c) Draw out the retrosynthetic analysis giving the disconnections that you consider the planners had in mind and label them suitably.
(d) What synthon does the starting material A represent?

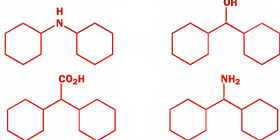
5. A synthesis of the enantiomerically pure ant pheromone is required. One suitable starting material might be the enantiomerically pure alkyl bromide shown. Suggest a synthesis of the pheromone based on this or another starting material.



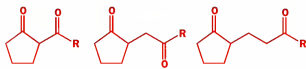
6. Show how the relationship between the alkene and the carboxylic acid influences your suggestions for a synthesis of these unsaturated acids.



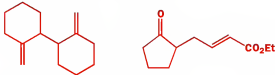
7. How would you make these compounds?



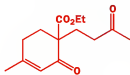
8. Show how the relationship between the two functional groups influences your suggestions for a synthesis of these diketones.



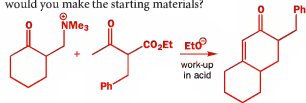
9. Suggest syntheses for these compounds. (Hint. Look out for a 1,4-dicarbonyl intermediate.)



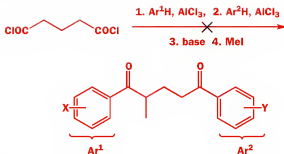
10. Suggest a synthesis of this diketo-ester from simple starting materials.



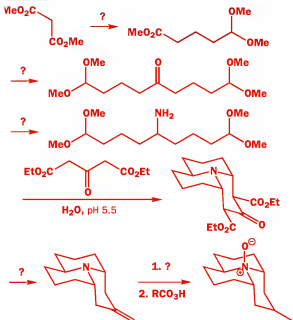
11. Explain what is happening in this reaction. Draw a scheme of retrosynthetic analysis corresponding to the synthesis. How would you make the starting materials?



12. These diketones with different aryl groups at the ends were needed for a photochemical experiment. The compounds could be prepared by successive Friedel-Crafts acylations with a diacid dichloride but the yields were poor. Why is this a bad method? Suggest a better synthesis.



13. This is a synthesis for the ladybird defence compound coccinelline.



Suggest reagents for the reactions marked '?' (several steps may be needed) and give mechanisms for those that are not.

14. Suggest syntheses for these compounds.

